Exh. 1

Cimetidine: does neurotoxicity occur? Report of three cases[1]

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There have been several reports of neurotoxicity attributed to cimetidine. These include confusion (Grimson 1977, Delaney & Raven 1977, McMillen *et al.* 1978, Wood *et al.* 1978) and twitching (Grave *et al.* 1977). In none have plasma cimetidine estimations been performed. Here we report three cases of neurotoxicity in which the plasma cimetidine concentration was estimated. Cimetidine was present in the CSF of two of the cases. The causative role of cimetidine is discussed.

Case 1

A 58-year-old woman with a past history of diverticulitis presented with lower abdominal pain. After a period of conservative management with antibiotics laparotomy was performed. A perforated pericolic abscess, generalized peritonitis, and subphrenic abscesses were found. The abscesses were drained and a transverse colostomy performed. Postoperative complications were pulmonary oedema, wound infection with faecal fistula formation and recurrent subphrenic abscess. Infection was treated with benzylpenicillin, metronidazole and gentamicin. Following exploration of the left subphrenic space she again developed pulmonary oedema and required temporary ventilation. She developed oliguria which, despite discontinuing gentamicin, progressed to anuria. Cimetidine syrup 200 mg six hourly was started following aspiration of blood via the nasogastric tube. She was haemodialysed for three weeks during which time she received cimetidine 200 mg eight hourly i.v. She was drowsy throughout. When spontaneous diuresis commenced, haemodialysis was stopped. Three days later she became confused and, following a right Jacksonian fit, developed status epilepticus. This was uncontrolled by diazepam 20 mg i.v., phenytoin 500 mg i.m., 10 ml 10% calcium gluconate and 2 ml 50% magnesium sulphate. Thiopentone 500 mg i.v. hourly was necessary to achieve control. At this time plasma sodium was 139, potassium 3.3, urea 20.0, glucose 6.3 mmol/l. CSF showed RBC 0, WBC 0, protein 0.12 g/l. CAT scan was normal. Plasma cimetidine concentration was 7.5 mg/l and CSF cimetidine concentration 0.82 mg/l (high pressure liquid chromatography method) (Randolph *et al.* 1977). She was also receiving benzylpenicillin 12 megaunits eight hourly i.v., gentamicin 60 mg i.v. daily (with plasma level monitoring) and metronidazole 2 g eight hourly per rectum for persistent sepsis. Metronidazole levels were low at 26.8 µg/ml (polarographic method) (Kane 1961). Cimetidine was reduced to 200 mg i.v. daily. Penicillin, gentamicin and metronidazole were stopped. She recovered consciousness and had no further fits. Subsequently renal function recovered but reexploration of the abdomen 2 months later revealed an adenocarcinoma of the left ovary and the patient subsequently died.

Case 2

A 73-year-old man with osteoarthritis, gout, psoriasis, hypertension and mild chronic renal failure, sustained a gastrointestinal bleed whilst an inpatient. He was on cimetidine 200 mg

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…hourly. Prior to this event his creatinine clearance was 13 ml/minute, urea 18.3 mmol/l and creatinine 256 μmol/l. He was transfused and started on cimetidine 200 mg eight hourly i.v. The next day he became confused and widespread muscular twitching was noted. Plasma cimetidine concentration was 1.53 mg/l 14 hours after his first dose of cimetidine. His urea was 19.7 mmol/l and creatinine 290 μmol/l. Cimetidine was reduced to 200 mg twice daily i.v. and on the third day of cimetidine therapy twitching was less noticeable and he was less confused. He continued to bleed, was further transfused and required urethral dilatation prior to catheterization. After this he had a good diuresis. On the fourth day the frequency and extent of the twitching had further lessened. Plasma cimetidine concentration (90 min after dose) was 1.37 mg/l. Urea was 31.0 mmol/l and creatinine 420 μmol/l. Following a further bleed later that day, he underwent gastroduodenotomy, vagotomy and oversewing of three pyloric ulcers. Postoperatively cimetidine was increased to 200 mg six hourly and on the next (fifth) day the twitching was again evident. At this time the plasma cimetidine concentration (90 min after dose) was 2.97 mg/l and urea had fallen to 28.0 mmol/l. On the sixth day cimetidine was reduced to 100 mg six hourly and the twitching was less evident. Plasma cimetidine concentration (2 h 30 min after dose) was 0.85 mg/l, urea 32.6 mmol/l and creatinine 301 μmol/l. No twitching was observed on the seventh day but at 18.00 that day the patient had a further melaena and cimetidine was increased to 200 mg eight hourly i.v. On the eighth day the patient became more confused but no further twitching was observed. Plasma cimetidine concentration (2 h 30 min after dose) was 1.04 mg/l, urea 20.0 mmol/l and creatinine 225 μmol/l. He was transfused again but after this had no further bleeds. On the fourteenth day the patient was changed to cimetidine 200 mg eight hourly orally. The plasma cimetidine concentration (90 min after dose) was 2.36 mg/l on the sixteenth day. By then the urea had fallen to 11.3 mmol/l and creatinine was 120 μmol/l, and the patient was no longer confused or twitching. The blood urea, creatinine and plasma cimetidine concentration during the clinical course of this patient are charted below (Figure 1). The patient has now recovered.

Case 2

A 62-year-old man was admitted to hospital with pneumococcal pneumonia which was treated with benzylpenicillin. Hypocalcaemia and tetany of unknown aetiology developed 24 hours

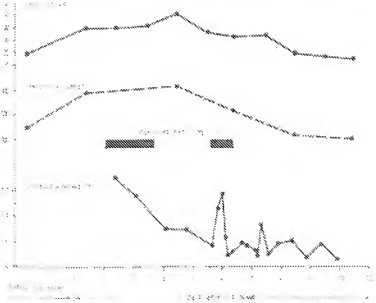

Figure 1. Cimetidine-induced twitching in renal failure. Blood urea, creatinine and plasma cimetidine concentration during clinical course of Case 1

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… with loss of abdominal pain … otomy was performed. … ulcers were found. The … postoperative complications … formation and recurrent … candidiasis and gentamicin … eloped pulmonary oedema … uch, despite discontinuing … early, was started following … sed for three weeks during … crosis throughout. When … three days later she became … ous epilepticus. This was … 1977, calcium gluconate and … was necessary to achieve … (2.07), glucose 6.3 mmol/l … normal. Plasma cimetidine … 3 mg/l (high pressure liquid … serving benzylpenicillin 1.2 … ium level monitorings and … theophylline levels were low … was reduced to 200 mg i.v. … e recovered consciousness … but reexploration of the … …ch ovary and the patient …

… on and mild chronic renal … from azapropazone 300 mg …

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after admission. This responded to 50 ml of 10% calcium gluconate, after which the plasma calcium concentration was 2.38 mmol/l. Two days after admission a diagnosis of pneumococcal meningitis was confirmed by lumbar puncture and he was given a single dose of 10 000 units of intrathecal penicillin. Acute renal failure developed concurrently and was treated with peritoneal dialysis.

Two days later, following a haematemesis, he was started on cimetidine 200 mg twice daily i.v. which was subsequently increased to 200 mg six hourly i.v. Twenty-four hours later (after 4 doses) he developed grand mal convulsions uncontrollable by conventional anticonvulsants. Control was obtained by curarization and intravenous infusion of thiopentone. Repeat lumbar puncture was unchanged. Plasma sodium, potassium, calcium and magnesium were all normal. Urea was 35.0 mmol/l. The plasma cimetidine concentration was 1.75 mg/l, CSF cimetidine concentration was 0.76 mg/l. Cimetidine was discontinued and after 24 hours no further convulsions occurred, although he did not fully regain consciousness. He subsequently developed pseudomonas septicaemia and died. Permission for autopsy was refused.

Discussion

Although the neurotoxicity described in these cases is multifactorial we believe cimetidine played an important role in Cases 1 and 2. In Case 1 in spite of renal impairment and sepsis we found no metabolic or infective cause for the convulsions. The dose of penicillin was not excessive. Metronidazole levels were low and we know of no reports of this agent causing convulsions. Plasma cimetidine concentration was high at 7.5 mg/l. (Normal range 2 hours after dose 0.5–3.0 mg/l). CSF cimetidine was 0.82 mg/l. Cimetidine accumulation occurred when haemodialysis was discontinued, as the usual route of elimination via the urine was not available. The drug is cleared well by haemodialysis (Canavan *et al.* 1977). In Case 2, the occurrence of twitching correlated with the plasma cimetidine concentration only whilst the patient was uraemic. There was no correlation between the plasma cimetidine concentration and mental confusion in this patient (see Figure 1). In Case 3 convulsions occurred only while the patient was on cimetidine; however, there is a 25 per cent incidence of convulsions in pneumococcal meningitis (Dodge & Swartz 1965), making a relationship to drug therapy appear less likely. In addition this patient was receiving penicillin. It is of interest to note, that cimetidine was detected in the CSF, and that the CSF plasma cimetidine ratio was 0.43, as compared to 0.11 in Case 1. This may not be surprising in view of the effect of meningitis on the permeability characteristics of the blood-brain barrier.

Increased permeability of the blood-brain barrier has also been reported in renal failure (Fishman & Raskin 1965, Smithers *et al.* 1975). This could explain why in Case 2 the comparatively high cimetidine level on the sixteenth day was not associated with twitching, as by this time the patient was not uraemic, and therefore less cimetidine would have crossed the blood-brain barrier.

Previous reports have linked cimetidine neurotoxicity and renal failure (McMillen *et al.* 1978, Wood *et al.* 1978). Grave *et al.* (1977) noted twitching in a man of 81 given cimetidine 200 mg six hourly i.v. for erosive gastritis following prostatectomy. At the time he was in renal failure with a blood urea of 21 mmol/l. It is of interest that no cases of neurotoxicity were reported in a large series of patients given cimetidine following renal transplantation (Jones *et al.* 1978).

There are no previous reports in the literature of cimetidine crossing the blood-brain barrier in man. Extensive toxicological and pharmacological studies in animals have failed to detect cimetidine in the central nervous system and neurotoxicity has not been noted (Brimblecombe & Duncan 1977, Leslie & Walker 1977, Cross 1977). The fact that hyperprolactinaemia can be induced by cimetidine (Delle Fave *et al.* 1977), suggests that the drug may cross the blood-brain barrier in certain circumstances. The precise mechanism for this effect remains unclear (Burland *et al.* 1979).

The cases presented in this report suggest that cimetidine may be neurotoxic in debilitated patients especially when the blood-brain barrier is compromised. Until there have been further studies correlating clinical signs with levels of cimetidine in blood and CSF, cimetidine should

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Summary
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Acknowledgments: W[illegible]
for permission to rep[illegible]
on plasma and CSF [illegible]
for their helpful comm[illegible]
estimations.

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Smithers J L, Nichols P J & [illegible]
Wood C A, Isaacson M L & [illegible]

...mdc, after which the plasma ... a diagnosis of pneumonia ... a single dose of 1 000 mg ... ously and was treated with

...imetidine 200 mg t.i.d.s. daily ... twenty-four hours later (after ... conventional anticonvulsant ... ethosuximide. Repeat urea ... m and magnesium were all ... was 1.75 mg/l. CSF ... and after 24 hours ... awareness. He subsequently ... opsy was refused.

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... be neurotoxic in debilitated ... Until there have been further ... and CSF, cimetidine should

be used with caution in renal impairment. Where renal impairment is significant the total cimetidine daily dosage should not exceed 800 mg, as is suggested in the official data sheet.

Summary
Three cases of encephalopathy associated with cimetidine therapy are presented. All three patients had impaired renal function and had received cimetidine in standard dosage. Measurable amounts of cimetidine were present in the CSF of two patients, confirming that the drug can cross the blood-brain barrier in man under certain circumstances. Where renal impairment is significant, the total daily dosage of the drug should be appropriately reduced.

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